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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR MONITORING DRUG ACTIVITIES *IN VIVO*

(57) Abstract: Methods, systems and equipment useful for monitoring *in vivo* activities of CCI-779 or other drugs. Numerous drug activity genes can be identified by the present invention. The expression profiles of these genes in peripheral blood mononuclear cells can be modulated by CCI-779 or other drugs. Therefore, these genes can be used as surrogate markers for monitoring drug activities *in vivo*.

WO 2004/072265 A3

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C07K16/18 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BURCZYNSKI ET AL.: "Pharmacogenomic expression profiling of renal cell carcinoma in a phase II trial of CCI-779: identification of surrogate markers of disease and predictors of outcome in the compartment of peripheral blood" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, November 2002 (2002-11), page S51, XP002295167 ISSN: 0959-8049 the whole document	1-5, 7-11,17, 18,20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2004	19.01.2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Hagenmaier, S

13

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHULZE-KOOPS H ET AL: "Persistent reduction in IL-6 mRNA in peripheral blood mononuclear cells of patients with rheumatoid arthritis after treatment with a monoclonal antibody to CD54 (ICAM-1)." CLINICAL AND EXPERIMENTAL IMMUNOLOGY. NOV 1996, vol. 106, no. 2, November 1996 (1996-11), pages 190-196, XP002295168 ISSN: 0009-9104	1,7-11, 17
Y	the whole document	2-5
X	DIPAOLA R S ET AL: "Phase I clinical and pharmacologic study of 13-cis-retinoic acid, interferon alfa, and paclitaxel in patients with prostate cancer and other advanced malignancies." JOURNAL OF CLINICAL ONCOLOGY : OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY. JUL 1999, vol. 17, no. 7, July 1999 (1999-07), pages 2213-2218, XP002295169 ISSN: 0732-183X	1,7-11, 17
Y	the whole document	2-5,18, 20
X	"Product Catalogue" January 2002 (2002-01), AFFYMETRIX , XP002295173 Human Genome U95Av2. page 1	18,20
X	SU A I ET AL: "Molecular classification of human carcinomas by use of gene expression signatures" CANCER RESEARCH 15 OCT 2001 UNITED STATES, vol. 61, no. 20, 15 October 2001 (2001-10-15), pages 7388-7393, XP002295170 ISSN: 0008-5472 See "Microarray Hybridization". page 7388, right-hand column, paragraph 2 & DATABASE SOURCE 2 Datasets contain expression data for Hs.125221 2 September 2004 (2004-09-02), http://genome-www5.stanford.edu/cgi-bin/source/expressionSearch?option=cluster&criteria=Hs.125221&organism=Hs abstract	18,20
Y	WO 02/40000 A (WYETH CORP) 23 May 2002 (2002-05-23) the whole document	1-5, 7-11,17, 18,20

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ELIT LAURIE: "CCI-779 Wyeth." CURRENT OPINION IN INVESTIGATIONAL DRUGS (LONDON, ENGLAND : 2000) AUG 2002, vol. 3, no. 8, August 2002 (2002-08), pages 1249-1253, XP008037562 ISSN: 1472-4472 page 1252, line 3 the whole document	1-5, 7-11,17, 18,20
Y	PERALBA JOSEP-MARIA ET AL: "Pharmacodynamic evaluation of the rapamycin ester CCI-779" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 43, March 2002 (2002-03), pages 1000-1001, XP001182924 & 93RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH; SAN FRANCISCO, CALIFORNIA, USA; APRIL 06-10, 2002 ISSN: 0197-016X the whole document	1-5, 7-11,17, 18,20
Y	RININGER J A ET AL: "Differential gene expression technologies for identifying surrogate markers of drug efficacy and toxicity" DRUG DISCOVERY TODAY 01 DEC 2000 UNITED KINGDOM, vol. 5, no. 12, 1 December 2000 (2000-12-01), pages 560-568, XP002295171 ISSN: 1359-6446 the whole document	1-5, 7-11,17, 18,20
Y	WO 00/40749 A (LIEW CHOONG CHIN) 13 July 2000 (2000-07-13) abstract page 3, line 23 - page 4, line 5 page 11, line 1 - line 16 page 14 - page 16; example 6 page 18 - page 19; example 8 claims 10-12,19-23	1-5, 7-11,17, 18,20
Y	WO 01/81916 A (CORNELL RES FOUNDATION; FERRAN CHRISTINE; VASCONCELLOS LAURO; SUTHANTH) 1 November 2001 (2001-11-01) claim 18 the whole document page 50	1-5, 7-11,17, 18,20

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	PERALBA JOSEP MARIA ET AL: "Pharmacodynamic Evaluation of CCI-779, an Inhibitor of mTOR, in Cancer Patients." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. 1 AUG 2003, vol. 9, no. 8, 1 August 2003 (2003-08-01), pages 2887-2892, XP002295172 ISSN: 1078-0432 the whole document	1-5, 7-11,17, 18,20
E,L	WO 2004/048933 A (STOVER JENNIFER A ; DORNER ANDREW (US); SLONI DONNA K (US); TWINE NATA) 10 June 2004 (2004-06-10) the whole document	1,4, 7-11,17

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US2004/004118

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6,14-16,19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

claims 1,2,5,6 (all partially); 3,4,7-11(all completely)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 6,14-16,19

Claims 14-16 refer to "qualifiers" from the "Qualifier Table". The table comprises up to 5000 different oligonucleotides (Seq.IDs 387-5278). However it is not clear from table 1 to which genes these "qualifiers" relate. Claims 14-16 are therefore considered to lack clarity and conciseness (Art. 6 PCT) to such an extent that a meaningful search for the subject matter claimed in claims 14-16 was impossible.

Present claim 19 relates to an extremely large number of possible kits which comprises a plurality of antibodies. In fact, the claim contains so many possible options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the whole scope of the claim impossible. Due to the fact that no such kit is exemplified in the application, the subject matter of claim 19 is considered that unclear and inconcise that a meaningful search was not possible for any kit encompassed by claim 19.

The following remark applies to the first invention; should further search fees be paid, similar remarks could apply in regard to the further inventions to be searched:
Present claim 6 relates to an extremely large number of possible methods. In fact, the claim contains so many possible options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the whole scope of the claim impossible. Due to the fact that no specific example is given in the application relating to at least two genes wherein one of the genes is the DKFZP564E1962 gene (see non-unity), the subject matter of claim 6 is considered that unclear and inconcise that a meaningful search was not possible for any method of claim 6 which relates to at least two genes wherein one of the genes is the DKFZP564E1962 gene.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1 (claims 1,2,5,6 (all partially); 3,4,7-11 (all completely)):

A method comprising comparing an expression profile of at least one gene in a peripheral blood sample of a patient to a reference profile of said gene which is differentially expressed in PBMCs of patients who have a non-blood disease and are subject to a drug therapy as compared to PBMCs isolated from said patients before said drug therapy and wherein the patient has the non-blood disease and is being treated by said drug therapy and wherein in particular the at least one gene is DKFZP564E1962, the non-blood disease is RCC and the drug is CCI-779.

Inventions 2-312 (claims 1,2,5,6 (all partially)):

A method comprising comparing an expression profile of at least one gene in a peripheral blood sample of a patient to a reference profile of said gene, wherein the at least one gene is ETR101 which is differentially expressed in PBMCs of patients who have a non-blood disease and are subject to CCI-779 therapy as compared to PBMCs isolated from said patients before said drug therapy.
..ibidem for Inventions 3-312 relating to a different gene selected from table 5.

Inventions 313-348 (claims 1,12 and 13 (all partially)):

A method according to claim 1, wherein said at least one gene is IL1R1 which is differentially expressed in PBMCs of patients who have a non-blood disease as compared to PBMCs of humans who do not have the non-blood disease, and wherein said drug therapy is capable of down-regulating or up-regulating expression of said one or more genes in PBMCs of patients who have the non-blood disease.
..ibidem for each gene listed in table 6.

Invention 349 (claims 1 and 13 (both partially)):

A method according to claim 1, wherein said at least one gene includes ATP2B1 whose expression in PBMCs is capable of being increased or reduced by a PHA treatment, and wherein said drug therapy is capable of down regulating or up-regulating expression of said one or more genes in phytohemagglutinin-treated PBMCs.

Invention 350 (claim 17 (completely)):

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of identifying drug activitiy genes, comprising: detecting an expression profile of genes in peripheral blood samples of patients having a non-blood disease and are subject to a drug therapy, and comparing said expression profile to a baseline expression profile of said genes in peripheral blood samples isolated from said patients before said drug therapy so as to identify drug activity genes whose expression levels in peripheral blood samples can be modulated by said drug therapy.

Invention 351 (claims 18-20 (all completely))

A kit comprising a plurality of polynucleotides, wherein each of said polynucleotides is capable of hybridizing under stringent or nucleic acid array hybridization conditions to an RNA transcript, or the complement thereof, of a different respective gene selected from table 5; a kit comprising a plurality of antibodies, wherein each of said antibodies is capable of binding to a polypeptide encoded by a different respective gene selected from table 5; a nucleic acid array comprising polynucleotide probes, wherein a substantial portion of all polypeptide probes on the nucleic acid array can hybridize under stringent or nucleic acid conditions to RNA transcripts, or the complements thereof, of genes selected from table 5.

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